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(54) Title: 5-HT_{1A} LIGANDS

(57) Abstract

Selective 5-HT_{1A}-antagonists radiolabelled with ^{3}H or ^{11}C are radiolabelled ligands useful, for example, in pharmacological screening procedures and in positron emission tomography (PET) studies.

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5-HT_{1A} ligands

This invention relates to certain 5-HT_{1A} ligands which are radiolabelled with ^{3}H or ^{11}C.

We have found that certain compounds which are 5-HT_{1A} ligands having specified characteristics can be labelled with with ^{3}H or ^{11}C to give radiolabelled ligands making them particularly useful in, for example, pharmacological screening procedures or in positron emission tomography (PET) studies. The 5-HT_{1A} ligands that are suitable for such radiolabelling are selective 5-HT_{1A} antagonists. By the term "selective 5-HT_{1A} antagonists" are meant compounds which:

(1) are highly potent ligands at the 5-HT_{1A} site having an IC_{50} value of 50nM or less (as determined by procedure A below).

(2) are at least 25 fold selective in terms of their IC_{50} values for the 5-HT_{1A} site compared with their IC_{50} values for other major monoamine receptor sites in the CNS (as determined by procedure B below).

(3) act as antagonists but not agonists in pharmacological models of 5-HT_{1A} receptor function (as determined by procedure C(a) or C(b) below).

Procedure (A)

The compounds are tested for the 5-HT_{1A} binding properties by measuring their ability to displace [^{3}H]-8-OH-DPAT from the 5-HT_{1A} receptor in rat hippocampal membranes according to the procedure of B.S. Alexander and M.D. Wood, J. Pharm. Pharmacol., 1988 40, 888-891. A compound is regarded as highly potent in this procedure if it has an IC_{50} of 50nM or less.

Procedure (B)

The affinity of the compounds for D_2 receptor sites is determined by the procedure of P. Seeman et al., J. Neurochem., 1984, 43, 221-235.

The affinity of the compound for α_1 sites is determined by the procedure of A.L. Morrow et al., Mol. Pharmacol., 1986, 29, 321.

The affinity of the compound for 5-HT_{2A} sites is determined by the procedure of R.A. Lyon et al., Mol. Pharmacol., 1987, 31, 194-199. (The 5-HT_{2A} site was previously known as the 5-HT_2 site).

A compound is regarded as being 25 fold selective if the IC_{50} value for each of the D_2, α_1 and 5-HT_{2A} sites as determined above is at least 25 times the IC_{50} value for the 5-HT_{1A} site as determined in Procedure (A). Preferably the compound should be 50 fold selective.

In addition to showing selectivity over the D_2, α_1 and 5-HT_{2A} sites it is also preferable that the compound is 25 fold selective (preferably 50 fold selective) over one or more of the 5-HT_{1B}, 5-HT_{2C}, 5-HT_{1D}, 5-HT_3, α_2, β and D_1 sites. The affinity for these sites is determined by the following procedures.

5-HT_{1B}: B.J. Alexander et al., Br. J. Pharmac., 1986, 87, P 22.

5-HT_{2C}: B.J. Alexander et al., Br. J. Pharmac., 1986, 87, P 22. (The 5-HT_{2C} site was previously known as the 5-HT_{1C} site).

5-HT_{1D}: C. Waeber et al., Naunyn-Schmiedebergs Arch. Pharmacol., 1988, 337, 595-601.

5-HT_3: N.M. Barnes et al., J. Pharm. Pharmacol., 1988, 40, 548-551.

α_2: D.J. Loftus et al., Life Sciences, 1984, 34, 61-69.

β: L.T. Williams and R. J. Lefkowitz (1987) Receptor binding studies in adrenergic pharmacology, Raven Press, New York.

D_1: V Billard et al., Life Sciences, 1984, 35, 1885-1893.

Procedure (C)

This procedure determines whether a compound that has 5-HT_{1A} binding activity (as determined by procedure (A) possesses agonist and/or antagonist activity. Brain 5-HT_{1A} receptors exist as two populations in the brain i.e. postsynaptic 5-HT_{1A} receptors and presynaptic somatodendritic 5-HT_{1A} receptors. The presynaptic

receptors are particularly sensitive to the agonist properties of 5-HT_{1A} receptor ligands and are activated by compounds designated 'partial agonists', which function as antagonists at the postsynaptic receptor. "Partial agonists" dose-dependently activate presynaptic receptors but "antagonists" do not display significant agonist activity in models of either postsynaptic or presynaptic 5-HT_{1A} receptor function but act as antagonists in both types of model. The activation of presynaptic 5-HT_{1A} receptors results in the inhibition of serotonin neurones which can be quantified in two ways:-

(a) Electrophysiologically monitoring the activity of the neurones to measure their firing rate by the method of H.J. Haigler and G.K. Aghajanian, J. Pharmacol. Exp. Therap., 1974, 188, 688. An intravenous ID_{50} dose is determined. The agonist, 8-OH-DPAT, has an ID_{50} value of 1.9 µg/kg iv. Antagonists are those compounds which meet criteria (1) and (2) above, which do not induce a 50% reduction in neuronal firing rate below a dose of 500 µg/kg iv and which significantly ($p < 0.05$) increase the ID_{50} of the agonist 8-OH-DPAT.

(b) Studying the effect on 5-HT release in the hippocampus using in vivo microdialysis according to the method of C. Routledge, J. Gurling. I. K. Wright and C.T. Dourish, Eur. J. Pharmacol. 239, 195-202, 107, 5P. Agonists and partial agonists significantly reduce 5-HT release following subcutaneous administration, whereas antagonists do not significantly decrease 5-HT release but antagonise the decreased release induced by 8-OH-DPAT.

The present invention provides a selective 5-HT_{1A}-antagonist (as hereinbefore defined) radio labelled with ^{3}H or ^{11}C.

Examples of suitable 5-HT_{1A}-antagonists which may be radiolabelled are described, for example, in GB-A-2255337, GB-A-2230780, GB-A-2230781 and GB-2248836. Particularly preferred compounds are

(a) N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)- N-(2-pyridinyl)cyclohexanecarboxamide and its pharmaceutically acceptable acid addition salts. The compound has an IC_{50} value of 2.2nM according to procedure (A). In procedure (B) the percentage inhibition of binding by the compound at 10^{-6}M was <50% at the following sites:- 5-HT_{1B}, 5-HT_{2C}, 5-HT_{1D}, 5-HT_{2A}, α_2, β, D_1, and D_2 (an inhibition of <50% at 10^{-6}M means that the binding affinity is very low). Its binding affinity at α_1, sites was 230 nM. In procedure (Ca) the compound does not induce 50% inhibition of firing up to

doses of 600 μg/kg iv. It significantly ($p<0.05$) increases the ID_{50} of 8-OH-DPAT. In procedure (Cb), the compound at 1 mg/kg s.c. did not significantly reduce 5-HT release in the hippocampus, indicating a lack of presynaptic 5-HT_{1A} receptor agonist activity. Pretreatment with compound (a) (at 0.1 - 1 mg/kg S.C) completely blocked the 8-OH-DPAT-induced decrease in 5-HT release demonstrating that the compound is an antagonist at the somatodendritic 5-HT_{1A} autoreceptor. Compound (a) is termed hereinafter WAY-100635.

(b) N-tert-butyl-3-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropanamide, its (+)-enantiomer and the pharmaceutically acceptable acid addition salts thereof. In procedure (A) the IC_{50} value for the racemate is 34 nM and that of the (+)-enantiomer is 15.5 nM. In procedure (B) the percentage inhibition of binding by the racemate and its (+)-enantiomer at 10^{-6}M was as follows:-

	% inhibition	
Binding Site	Racemate	(+)-Compound
5-HT_{1B}	27	22
5-HT_{2C}	37	50
5-HT_{2A}	37	61
α_1	*	**
α_2	10	11
β	20	12
D_1	20	22
D_2	14	20

*IC_{50} = 1491 nM

**IC_{50} = 1878 nM

In Procedure (Ca) the racemate and the (+)-enantiomer do not induce 50% inhibition of firing up to doses of respectively 2500 and 600 μg/kg iv. At doses of 500 μg/kg iv these compounds significantly ($p<0.05$) increase the ID_{50} of 8-OH-DPAT. In procedure (Cb), the racemate and its (+)-enantiomer (both at 10 mg/kg s.c.) had no significant effect on extracellular levels of 5-HT in the hippocampus demonstrating that these compounds are devoid of 5-HT_{1A} receptor agonist properties. Pretreatment with the racemate (at 10 mg/kg s.c.) and (+)-compound (b) (at 1-10 mg/kg s.c.) completely blocked the 8-OH-DPAT-induced decrease in 5-HT release demonstrating that these compounds are antagonists at the somatodendritic 5-HT_{1A} autoreceptor.

(c) R-[(-)-2,3,4,5,6,7-hexahydro-1-4-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylbutyryl-1H-azepine and the pharmaceutically acceptable acid addition salts thereof. The IC_{50} value in procedure (A) is 0.3 nM. In procedure (B) the percentage inhibition of binding by the compound at 10^{-6} M was <50% at the following sites: 5-HT_{1B}, 5-HT_{2C}, β and D_1. The percentage inhibition of binding by the compound at 10^{-6}M was 53% at α_2 sites. The IC_{50} values at 5-HT_{1D}, 5-HT_{2A}, α_1 and D_2 sites was 2240 nM, 106 nM, 53 nM and 277 nM respectively.

In procedure (Cb), the compound at 1 mg/kg s.c. had no significant effect on extracellular levels of 5-HT in the hippocampus demonstrating that the compound is devoid of 5-HT_{1A} receptor agonist properties. Pretreatment with the compound (1 mg/kg s.c.) completely blocked the 8-OH-DPAT-induced decrease in 5-HT release demonstrating that the compound is an antagonist at the somatodendritic 5-HT_{1A} autoreceptor.

Accordingly a preferred embodiment of the invention comprises a compound selected from the group consisting of N-(2-(1-(4-(2-methoxyphenyl)-piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide, N-tert-butyl-3-[4-(2-methoxyphenyl)-piperazinyl]-2-phenylpropanamide or its (+)-enantiomer and R-[(-)-2,3,4,5,6,7-hexahydro-1-4-[1-[4-(2-methoxyphenyl)-piperazinyl]]2-phenylbutyryl-1H-azepine and the pharmaceutically acceptable acid addition salts thereof, said compound being radiolabelled with ^3H or ^{11}C.

Selective 5-HT_{1A}-antagonists radiolabelled with ^3H are useful as standard ligands for studying 5-HT_{1A} binding in pharmacological test procedures. For example they may be used in a similar manner to [^3H]-8-OH-DPAT (as described in Procedure A above) in measuring the binding properties of other potential 5-HT_{1A} ligands. They have the advantage that they may be used in defining 5-HT_{1A} ligands as agonists or antagonists at an early stage of screening i.e. before having to do more time-consuming functional studies.

[^3H]WAY-100635 has been found to interact with a single class of recognition sites in rat hippocampal membranes. The ligand saturation equilibrium dissociation constant was 0.40±0.05 nM and the kinetically derived value was 0.33 nM. [^3H]WAY-100635 binding was reversible and the data support first order dissociation kinetics. The pharmacological binding profile of [^3H]WAY-100635 was consistent with recognition of the 5-HT_{1A} binding site. WAY-100635 showed

the highest potency (IC_{50}=3 nM) in inhibiting the binding of [^{3}H]WAY-100635. The 5-HT1A antagonist, SDZ-216525, also displayed high potency (IC_{50}=5 nM) at hippocampal [^{3}H]WAY-100635 binding sites. NAN190, 5-CT, 5-HT, 8-OH-DPAT, BMY7378, methiothepin and RU24969 were intermediate in potency (IC_{50}=10-100 nM) and PAPP, spiperone, ipsapirone, buspirone, gepirone and ritanserin displayed even weaker inhibition potencies (IC_{50}=100 nM-10 μM). Cyanopindolol, (-)propranolol, rauwolscine, yohimbine and clonidine displayed comparatively low potencies (IC_{50}=100 nM-100 μM) against [^{3}H]WAY-100635. The 5-HT uptake bloker, fluvoxamine, was inactive at micromolar concentrations against [^{3}H]WAY-100635 binding. Furthermore, noradrenaline, L-phenylephrine, isoprenaline, dopamine and atropine, all at a concentration of 10 μM, were ineffective at displacing hippocampal [^{3}H]WAY-100635 binding, as were clonazepam and imipramine.

Correlation plots of drug potencies (IC_{50} values) for the inhibition of [^{3}H]WAY-100635 binding to the human 5-HT_{1A} receptor (stably transfected into the Chinese Hamster Ovary cell line) and the rat hippocampal 5-HT_{1A} receptor produced correlation coefficient values close to unity ($r=0.96$: $P<0.001$, $DF=12$), revealing a significant agreement between the pharmacological profiles of both human and rodent 5-HT_{1A} binding sites.

Radioreceptor autoradiographic studies using rat brain sections demonstrated that the regional distribution of [^{3}H]WAY-100635 parallelled that of the high-affinity binding component of [^{3}H]8-OH-DPAT, a selective 5-HT_{1A} agonist. [^{3}H]WAY-100635 labels both agonist high- and low-affinity components of the 5-HT_{1A} receptor with equal affinity. [^{3}H]WAY-100635 can be used as a tool to label multiple affinity states of the 5-HT_{1A} receptor and to characterise agonist-mediated receptor-effector coupling mechanisms.

Selective 5-HT_{1A} antagonists radiolabelled with ^{11}C are useful as radioligands in Positron Emission Tomography (PET) studies. Such studies are carried out in vivo in animals and more preferably in humans. The ^{11}C serves as a positron source producing gamma rays. These rays are detected by the PET scanner and the resulting data is processed by computer so as to give information on the distribution of the radioligand in the living subject. There have been previous suggestions for studying the 5-HT system with PET by using radioligands for the various pre- and post-synaptic 5-HT receptors and binding sites. However previously no suitable radioligands have been available for the 5-HT_{1A} site.

The ^{11}C radiolabelled selective 5-HT_{1A} antagonist may be used in the PET studies as for example, a research tool or as a diagnostic aid. For example, the potency and duration of an orally or parenterally administered unlabelled drug, which is a 5-HT_{1A} ligand, can be measured by following the displacement of the ^{11}C labelled selective 5-HT_{1A}-antagonist from the brain of humans. Furthermore PET studies using ^{11}C radiolabelled selective 5-HT_{1A} ligands can be used to study the distribution and nature of 5-HT_{1A} receptor sites as a function of disease states (e.g. Alzheimer's Disease or depression) and hence can be used to diagnose such disease states.

The ^{3}H and ^{11}C radiolabelled selective 5-HT_{1A} antagonists may be prepared by methods known in the art. For example a precursor of the antagonist may be reacted with a ^{3}H or ^{11}C containing reagent such that the radioisotope is incorporated into the resulting molecule of the antagonist. For example an ethylenically unsaturated precursor may be catalytically hydrogenated with tritium to provide the ^{3}H- radiolabelled selective 5-HT_{1A} antagonist. In a further example a phenol precursor of an antagonist may be alkylated with a radiolabelled alkylating agent, e.g. [^{3}H]methyl iodide or [^{11}C]methyl iodide to provide the antagonist containing a radiolabelled methoxy substituted phenyl group. The [^{11}C]methyl iodide may be produced via [^{11}C]methanol from cyclotron-produced [^{11}C]carbon dioxide. The particularly preferred compounds (a), (b) and (c) mentioned above all contain a methoxyphenyl group and hence the radiolabelled compounds may be prepared from the phenol precursors. For example N-(2-(4-(2-hydroxyphenyl)-1-piperazinyl))ethyl)-N-(2-pyridyl)cyclohexane carboxamide may be alkylated with [^{3}H]- or [^{11}C]-methyliodide to give ^{3}H or ^{11}C labelled N-(2-(1-(4-(2-methoxyphenyl))-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide.

The following Examples illustrate the invention.

Example 1

[Methoxy-^{3}H] N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))-ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide

Sodium hydride (3 mg) was added to a solution of N-(2-(1-(4-(2-hydroxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide (8 mg) in DMF (1.5 ml) and the solution stirred at room temperature under nitrogen for 2 hours. [^{3}H]Methyl iodide (1 Ci) was distilled into the reaction mixture which was stirred at room temperature for 1.5 hours. The reaction mixture was then pumped to dryness on the manifold and taken to dryness several times with ethanol. The yield of crude material was 480 mCi.

The crude material was purified by preparative TLC (ethyl acetate:ethanol:triethylamine=100:12.5:0.5) on silica plates. The final yield of product was 132 mCi, at a specific activity of 71 Ci/mmol.

Example 2

[Methoxy-^{11}C] N-(2-(1-(4-(2-methoxyphenyl)-piperazinyl))-ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide

In a suitable manifold, sodium hydride (3 mg) was added to a solution of N-(2-(1-(4-(2-hydroxyphenyl)-piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexane-carboxamide (8 mg) in dimethyl formamide (1.5 ml) under nitrogen. [^{11}C]-Methyl iodide was distilled into the reaction mixture and the reaction heated to 80° C for 5 min. After purification by HPLC (Beckman Ultrasphere 5µ ODS (25 x 46 cm) 0.02M potassium dihydrogen orthophosphate:acetonitrile) the material was formulated for iv injection by dissolution in normal saline and sterile millipore filtration.

CLAIMS

1. A selective 5-HT_{1A} antagonist radiolabelled with ^{3}H or ^{11}C.

2. A compound as claimed in claim 1 wherein the selective 5-HT_{1A} antagonist is N-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl)-N-(2-pyridinyl)-cyclohexanecarboxamide, N-tert-butyl-3-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropanamide or its (+)-enantiomer or R-(-)-2,3,4,5,6,7-hexahydro-1-4-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylbutyryl-1H-azepine

or a pharmaceutically acceptable salt thereof.

3. [Methoxy-^{3}H] N-(2-(1-(4-(2-methoxyphenyl)-piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexane-carboxamide or a pharmaceutically acceptable salt thereof.

4. [Methoxy-^{11}C] N-(2-(1-(4-(2-methoxyphenyl)-piperazinyl))ethyl)-N-(2-pyridinyl)cyclohexane-carboxamide or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Int. .onal Application No
PCT/GB 94/00324

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K51/04 A61K49/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EUROPEAN JOURNAL OF PHARMACOLOGY, vol.187, no.2, 9 October 1990 pages 209 - 223 H. SIJBESMA ET AL. 'THE ANTI-AGGRESSIVE DRUG ELTOPRAZINE PREFERENTIALLY BINDS TO 5-HT1A AND 5-HT1B RECEPTOR SUBTYPES IN RAT BRAIN: SENSITIVITY TO GUANINE NUCLEOTIDES.' see page 220, left column, paragraph 1 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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1

Date of the actual completion of the international search	Date of mailing of the international search report
31 May 1994	16. 06. 94
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	CHEMICAL ABSTRACTS, vol. 114, no. 3, 21 January 1991, Columbus, Ohio, US; abstract no. 17928d, see abstract & BRAIN RES., vol.532, no.1, 1990 pages 191 - 196 RYDELEK-FITZGERALD L. ET AL. 'NAN-190: AGONIST AND ANTAGONIST INTERACTIONS WITH BRAIN 5-HT1A RECEPTORS.' ---	1-4
X	DATABASE MEDLINE US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US AN=88089658 see abstract & J. NEUROCHEM, vol.50, no.2, February 1988 pages 528 - 533 HERRICK-DAVIS K. '[3H]SPIROXATRINE: A 5-HT1A RADIOLIGAND WITH AGONIST BINDING PROPERTIES' ---	1
X	CHEMICAL ABSTRACTS, vol. 114, no. 25, 24 June 1991, Columbus, Ohio, US; abstract no. 240437p, see abstract & PHARMACOL., BIOCHEM. BEHAV., vol.38, no.3, 1991 pages 555 - 559 LINDA M. LIAU ET AL. 'CHARACTERIZATION OF A NOVEL AND POTENT 5-HADROXYTRYPTAMINE1A RECEPTOR ANTAGONIST.' ---	1
Y	CHEMICAL ABSTRACTS, vol. 117, no. 11, 14 September 1992, Columbus, Ohio, US; abstract no. 103411y, see abstract & DRUG DEV. RES., vol.26, no.3, 1992 pages 251 - 274 RICHARD A. GLENNON 'CONCEPTS FOR THE DESIGN OF 5-HT1A SEROTONIN AGONISTS AND ANTAGONISTS.' --- -/--	1-4

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US AN=93:472807 see abstract & 206TH ACS (AMER. CHEM. SOC.) NATIONAL MEETING,, 22 August 1993, CHICAGO page 206 CLIFFE I A 'THE DESIGN OF SELECTIVE 5-HT-1A RECEPTOR ANTAGONISTS. ABSTR PAP AM CHEM SOC' ----	1-4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB94/00324

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
In view of the large number of compounds, which are defined by the general definition of claim 1, the search had to be restricted for economic reasons The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims,....(please see annex)

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

BOX I.2.:

...and to the general idea underlying the application (see guidelines, Part B, Chapter III, paragraph 3.6).